UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,935	12/21/2000	Timothy Raymond Hirst	34407-503	8699

30623 7590 10/15/2009

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
10/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/674,935	HIRST ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,41,42,44,54,55,58,59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,41,42,44,54,55,58,59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/17/09 & 8/12/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The amendment filed September 17, 2009 has been entered. Claims 38, 44, 54-55, 58, and 61 have been amended. Claims 1-37, 39-40, 43, 45-53, 56-57, 60 and 62-68 are cancelled. Claims 38, 41-42, 44, 54-55, 58-59 and 61 are under consideration in this office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on August 12, 2009 and September 17, 2009 were filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Withdrawal of Rejections and Objections

3. The following rejections and objections have been withdrawn in view of applicants' amendments and arguments:

a) The rejection of claims 38-39, 41-42, 44, 49, 51-52 and 54-64 under 35 U.S.C. 103(a) as being unpatentable over Williams et al., (WO 97/02045 published January 23, 1997) in view of Hazama et al., (Immunology, 1993); and

b) The new matter rejection of claims 38-39, 41-42, 44, 49 and 51-52 under 35 U.S.C. 112, first paragraph.

Response to Arguments

4. Applicant's arguments with respect to claims 38, 41-42, 44, 54-55, 58-59 and 61 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection Necessitated By Amendments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 38, 41-42, 44, 54-55, 58-59 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richards et al., (1997. Vaccine. Vol. 15(10): 1065-1069) in view of Williams et al., (WO 97/02045 published January 23, 1997).

Claim 38 is drawn to a method of enhancing generating a T-lymphocyte mediated-immune response against a herpes virus infection in a mammal in need thereof, comprising co-administering to the mammal a therapeutically effective amount of Escherichia coli heat labile enterotoxin B subunit (EtxB), and an antigen, wherein the EtxB is free from whole toxin and is not linked to the antigen, wherein the antigen is a virus antigen from the herpes virus family, immune response against a herpes virus infection.

Claim 54 is drawn to a method of generating a T lymphocyte mediated immune response against an infection, in a mammal in need thereof, comprising administering to the mammal between 50 and 100 ug of subunit EtxB, wherein the EtxB is free from whole toxin and an antigen, wherein the EtxB and antigenic are not linked to form a single active agent.

Claims 41 and 58 are drawn to the virus antigen being selected from the group consisting of Herpes Simplex Virus- 1 (HSV- 1), Herpes Simplex Virus-2 (HSV-2), Epstein-Barr Virus (EBV), Varicella-zoster Virus (VZV), Cytomegalovirus (CMV), Human Herpes Virus-6 (HHV-6), Human Herpes Virus-7 (HHV-7) and Human Herpes Virus-8 (HHV-8). Claims 42 and 59 are drawn to the virus antigen being selected from the group consisting of HSV- 1, HSV-2, CMV or EBV.

Claims 55 and 61 are drawn to administration in multiple doses. Claim 44 is drawn to the EtxB and antigen being administered to the said mammalian subject in an amount which is effective to increase the mammalian subject's levels of T cell lymphocyte response to the antigen.

Richards et al., teach enhancement of a mucosal immune response to Herpes Simplex 1 Virus (HSV-1) in the presence of cholera toxin. Richards et al., teach the Herpes simplex virus antigen as protection from infection and provides effective immune responses, including mucosal immunity (page 1065, col.1). Richards et al., teach methods of enhancing the immune response to poorly immunogenic viral antigens include the use of mucosal adjuvants such as cholera toxin which is capable of

generating high levels of mucosal IgA and T cell responses (page 1065, col.2). The inoculation procedures show the Cholera toxin or subunit B toxin were co-administered with the virus antigen from HSV-1 (page 1066, col.1). Richards et al., teach the enhancement of anti-viral antibody response with the co-administration of Cholera toxin (page 1067,col.1). Richards et al., broad mucosal immune response with the application of viral antigens together with the cholera toxin eases administration and makes mucosal vaccines desirable (page 1067, col.1). However, Richards et al., do not use the *E.coli* heat labile enterotoxin (ExtB).

Williams et al., teach therapeutic agents for use in the treatment of mammalian diseases (page 1, line 35 – page 2, line 2). The basis of the invention is that the pure B-subunit of *E.coli* heat labile enterotoxin (ExtB) binds to receptors found on the surface of mammalian cells and this binding induces differential immune response effects on lymphocytes including activation of T cells (page 2, lines 1-5). The acronym, Ctx means Cholera toxin, CtxB means the pure B subunit while ExtB means the pure B subunit of *E.coli* heat labile enterotoxin (page 1, lines 26-36). Williams et al., teach the administration of Ctx, CtxB, Etx or EtxB as being interchangeable (page 4, lines 9-13). Williams et al., teach co-administration of the therapeutic agent, which is ExtB and the antigenic determinant, thereby teaching separate administration of the moieties (pages 3-4, lines 5-3). Williams et al., teach CtxB and EtxB have already been suggested as "vaccine carriers" and it is the basis for this effect, in part, of the ability of EtxB to modulate lymphocyte populations (as discussed above) by binding to the GM-1 receptor (page 10, lines 9-14). Williams et al., teach the ExtB as a vaccine carrier because of its

ability to modulate lymphocyte populations (page 10, lines 9-13). Williams et al., teach the agent is capable of modulating the immune response when delivered together with an unrelated foreign antigenic determinant and the antigen and agent are delivered together as separate moieties (page 10, lines 22-33). Williams et al., teach co-administration and separate administrations which occur at the same time (page 8, lines 7-13). Williams et al., teach that the wild type and mutant forms of ExtB have binding capabilities and are known as immunomodulators (page 11, line 31- page 12, line 5). Williams et al., teach the administration of EtxB or ExtB mutants to mice (page 14, lines 25-27). The results were expressed as mean IgG and IgA antibody titers in serum, wherein the results indicated an enhanced immune response by the antibodies, see Figure 2. Figure 3 teaches the kinetics of lymphocyte proliferation where the mice were injected with 30ug of a mutant version of ExtB (page 14, line 35- page 15 line 10). Williams et al., teach the injected amounts of ExtB are effective to enhance the level of the immune response. Figure 4 teaches that immunization with either pure or mutated ExtB caused an increased activation in B cells in the amount of 80ug/ml.

Therefore, it would have been prima facie obvious at the time of applicants invention to modify the method of generating a T lymphocyte mediated immune response against a herpes virus infection in a mammal comprising administering a mucosal adjuvant and an HSV-1 antigen as taught by Richards et al., wherein the modification exchange *E.coli* heat labile enterotoxin (ExtB) as taught by Williams et al., since Williams et al., teach they are interchangeable, both having GM-1 binding activity

and they are equivalent proteins. No more than routine skilled would have been required to prepare the co-administered therapeutically effective EtxB and the HSV-1 antigen when both Richards et al., and Williams et al, teach generating a T lymphocyte immune response against HSV in a mammal comprising co-administering or administration in conjunction with EtxB and the HSV antigen to no only induce immune response effects on lymphocytes including activation T cells but also provide protective immunity against a Herpes virus, as taught by Richards et al. Furthermore, one of ordinary skill in the art would have had a reasonable expectation of success in modifying the method of generation when only routine skill is required to exchange the mucosal adjuvant CtxB for ExtB when the art already teaches CtxB and EtxB are functionally equivalent, can be used interchangeably and ExtB potentiates local antibody and T lymphocyte responses to co-administered Herpes virus antigens.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 38, 41-42, 44 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "enhancing" in claim 38 is a relative term which renders the claim indefinite. The term "enhancing" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the

art would not be reasonably apprised of the scope of the invention. The meets and bounds of "enhancing the T-lymphocyte mediated immune response is not defined and there is no standard by which the enhancement is compared too. Therefore clarification is required to overcome the rejection.

Claim Objections

7. Claims 58-59 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 58-59 appear to duplicative of claims 41 and 42, because both sets of claims are dependant upon claim 38 and recite identical language. Therefore clarification is required to overcome the objection.

Conclusion

8. No claims allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645